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Pregnancy-Associated Melanoma Occurring in Two Generations

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We report of a case of malignant melanoma occurring during pregnancy in a woman whose mother had a melanoma excised during pregnancy. There was no other family history of melanoma. To our knowledge, this has not been previously reported. A review of the recent literature suggests that pregnant women with melanoma do not have a worse prognosis when compared to matched controls, but may present with worse prognostic features.
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KEY WORDS: melanoma; pregnancy; prognosis; familial; depth

INTRODUCTION

Men and women are equally affected with cutaneous melanoma. The median age at diagnosis is 54. Approximately 30% of melanoma patients are women in their reproductive years [1]. Melanoma occurring during pregnancy is an uncommon, but not rare, disease [2].

Familial melanoma was first described by Sir William Norris in 1820 when he observed a patient and his father affected with the disease [3]. It has been estimated that about 10% of melanoma patients have an affected family member [4]. Up to 44% of cases of multiple melanomas can be classified as familial [5]. Some cases are known to occur as part of the dysplastic nevi syndrome (DNS), also known as the familial atypical multiple mole and melanoma syndrome (FAMMM). Patients with FAMMM are at high risk for the development of cutaneous melanoma. Typically, these patients have a large number of atypical moles with dysplastic histological features [4].

We report a case of pregnancy-associated melanoma in a mother and daughter. This occurred in a 29-year-old woman who presented with metastatic melanoma in an inguinal lymph node during her first trimester of pregnancy. Interestingly, her mother had been treated for a pregnancy-associated melanoma 30 years previously. There was no history of DNS in the patient or her family. To our knowledge, there are no previous reports of pregnancy-associated melanoma occurring in two generations.

CASE REPORT

The patient was referred to Memorial Sloan-Kettering Cancer Center (MSKCC) in June 1994 for treatment of metastatic melanoma to a left inguinal lymph node. She had noted a mass in her left groin during the first month of pregnancy. This was initially treated with antibiotics. When it continued to enlarge, a lymph node biopsy was performed, which revealed metastatic melanoma. The patient had no prior history of melanoma. However, she had undergone excision biopsy of a pigmented lesion of her left posterior calf in 1986, which was interpreted as a compound nevus. On re-review at MSKCC, a diagnosis of invasive melanoma, 1.24 mm in depth, was made. The patient had undergone an elective abortion prior to presenting for surgical management of her inguinal disease. The patient had a 2-year-old child and had two miscarriages between 1990 and 1991. Interestingly, during both pregnancies, the patient developed pigmented lesions that disappeared after the miscarriages. Her family history was notable for a mother who had been diagnosed with melanoma during pregnancy at age 27, which was removed without subsequent recurrence. During a pregnancy in 1991, the patient had a benign mole removed from her left labia.

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TABLE I. Published Series Comparing Pregnant Vs. Nonpregnant Patients with Melanoma for Survival and Known Prognostic Factors*

Study	No. patients	Controls	Overall survival[a]	Prognostic factors (P vs. C)
Houghton et al. [12]	12	Age, site, stage	ND	More truncal sites (50% vs. 32%)
Reintgen et al. [1]	58	Clark's level, ulceration, depth	ND	More ulcerated lesions (21% vs. 15%) Deeper primaries (1.9 vs. 1.51)
Wong et al. [13]	66	Depth, site	ND	More truncal sites (41% vs. 15%)
Slingluff et al. [14]	100	Depth, site, Clark's level	ND	Fewer axial sites (trunk and head and neck) Deeper primaries (2.17 vs. 1.52, $P = 0.052$)
Mackie et al. [15]	92	Depth	ND	Deeper primaries (2.38 vs. 1.96, $P = 0.002$)
Travers et al. [16]	45	Nonmatched	ND	Deeper primaries (2.28 vs. 1.22, $P < 0.007$)

*P, pregnant group; C, control group; ND, no difference.
[a]Comparing nonpregnant control group to pregnant patients.

On examination, she appeared well, with a fair complexion, blue eyes, red hair, and multiple ephelides. The patient had a well-healed lymph node biopsy site overlying the left groin without residual lymphadenopathy. Examination of her left extremity revealed no evidence of locally recurrent melanoma or popliteal adenopathy. There was no evidence of in-transit disease. Examination of her remaining skin surface revealed no pigmented lesions of concern.

The patient had a normal chest X-ray, complete blood count (CBC), and liver function studies. She was taken to the operating room and underwent a wide excision of the biopsy site on her left calf and an inguinofemoral lymphadenectomy. The skin reexcision showed no residual melanoma. All of 12 lymph nodes were negative for tumor. The patient was started on adjuvant immunotherapy and received four injections of an investigational vaccine. She did not complete the protocol, however, due to side effects. She remained free of disease until May 1995 when she presented with recurrent melanoma in the lymph nodes distal to Hunter's canal. One month later, she developed widespread metastatic disease in the soft tissue and bone. The patient was treated with chemotherapy but died of her disease in July 1996.

DISCUSSION AND REVIEW OF THE LITERATURE

The effect that pregnancy has on the prognosis of a patient with malignant melanoma remains a topic of controversy. Evidence suggests that exposure to endogenous female hormones affects the development and progression of malignant melanoma. Although female sex is considered a favorable prognostic factor in patients with early-stage disease, this advantage disappears in patients with stage III and IV melanoma [6]. During pregnancy, there is an increased level of estrogen, progesterone, and melanocyte-stimulating hormone. Pigmentary changes are known to occur, with hyperpigmentation found to some degree in 91% of pregnant women [7]. Melasma, the "mask of pregnancy," consists of a blotchy irregular hyperpigmentation affecting the face in different patterns. It affects 46% of pregnant women [7]. Other investigators have demonstrated that melanocytic nevi excised during pregnancy have an increased number of cellular estrogen and progesterone receptors compared to nevi from women who were not pregnant or taking oral contraceptive pills [8].

Most of the initial studies that examined survival in patients with pregnancy-associated melanoma suggested that the prognosis was worse than that of nonpregnant patients [9,10]. Other studies were less conclusive, so the controversy continued [11]. More recently, well-controlled retrospective studies have been reported (Table I). In all of these studies, the investigators found no difference in survival between pregnant patients and nonpregnant controls. Interestingly, Houghton et al. [12] found that the survival rate in patients who were pregnant when diagnosed was less favorable than that for nonpregnant patients (55% vs. 83%, respectively). However, when the survival of the 12 pregnant patients was compared to controls matched for age, anatomic site, and stage, there was no difference between the two groups [12]. This suggested that pregnancy in melanoma patients was associated with less favorable clinical features at presentation. This was also reported in a study by Mackie et al. [15]. They found a less favorable survival in pregnant patients with melanoma until controlling for tumor thickness, after which the survival disadvantage was no longer apparent.

Travers et al. [16] reported that patients with pregnancy-associated melanoma presented with deeper primary tumors than nonpregnant women (2.28 vs. 1.22 mm, $P < 0.007$). In addition, Mackie et al. [15] reported that pregnant patients with melanoma presented with thicker tumors than nonpregnant patients (2.38 vs. 1.96 mm, $P = 0.002$). In our recent experience, the median depth at presentation of more than 500 nonpregnant patients with cutaneous melanoma was 1.1 mm (Brady et al., unpublished data). The reason that pregnant patients present with deeper primary lesions may be due to the

fact that changes in preexisting nevi as well as the appearance of new pigmented lesions during pregnancy are not uncommon. Alternatively, hormones associated with pregnancy may be trophic for melanocytic lesions. This is supported by murine studies that demonstrate an increased number of pulmonary metastases in pregnant vs. nonpregnant mice injected with a poorly differentiated melanoma cell line [17].

Other clinical features that are associated with a less favorable outcome appear to occur more commonly in pregnant patients with melanoma. These include truncal primary site [12,13] and the presence of ulceration of the primary lesion [1].

We report an interesting case of pregnancy-associated melanoma occurring in the daughter of a woman previously treated for melanoma occurring during pregnancy. This has not been previously reported in the absence of a history of DNS. Whether this is due to a genetic predisposition or merely a coincidence cannot be determined. A review of the recent literature suggests that patients who are diagnosed with melanoma during pregnancy do no worse than case-matched nonpregnant controls. However, they tend to present with less favorable pathological and clinical features.

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